UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,390	02/01/2002	Hal S. Padgett	P-LG 4878	4639

27860 7590 12/29/2005

LARGE SCALE BIOLOGY CORPORATION
3333 VACA VALLEY PARKWAY
SUITE 1000
VACAVILLE, CA 95688

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,390	PADGETT ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-72,78-83,85 and 87-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-72,78-, 83, 85 and 87-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/15/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 66-72, 78-83, 85 and 87-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The amendment to claims 66 and 67 of "defined composition containing enzymes wherein the enzymes consist essentially of" is apparently new matter. A careful review by the examiner of the specification failed to identify any support for this new limitation. The phrase never appears in the specification. This is particularly evident since the phrase "defined composition" itself lacks any definition. In reviewing the specification, the examples demonstrate that a "defined composition" can be something other than a homogenously purified protein as shown at page 57 of the specification, where the CEL-I is simply drawn to fractions which have CEL-I activity (see page 57, lines 14-20). Example 9, which uses

cloned CEL-I does not differentiate this issue because there is no indication that the enzyme was purified to a greater degree than in Example 1. As noted by the Federal Circuit in In re Wright, 9 USPQ2d 1649, 1650 (Fed. Cir. 1989) "We shall sustain this rejection. We agree with appellant that the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112. Nonetheless, the question remains as to whether the meaning of "not permanently fixed thereto" is sufficiently described in the specification to inform the public what said language is intended to encompass. From our review of the present disclosure, we are convinced that this limitation is subject to different interpretations and the specification is devoid of adequate guidelines to direct the public to the correct meaning."

The situation in Wright is precisely analogous to the current situation since the phrase "defined composition" is not sufficiently described to inform the public what compositions are "defined" and what compositions are not "defined". Apparently, Applicant would argue that a cell extract is "undefined" while a column fraction is "defined". In neither case is the composition limited to a homogenously purified set of components, all of which could be identified, which is closer to what the ordinary practitioner would understand "defined" to mean.

Since no basis has been found to support the new claim limitation in the specification, the claim is rejected as incorporating new matter.

3. Claims 66-72, 78-83, 85 and 87-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "defined composition containing enzymes wherein the enzymes consist essentially of". In reviewing the specification, the examples demonstrate that a "defined composition" can be something other than a homogenously purified protein as shown at page 57 of the specification, where the CEL-I is simply drawn to fractions which have CEL-I activity (see page 57, lines 14-20). Example 9, which uses cloned CEL-I does not differentiate this issue because there is no indication that the enzyme was purified to a greater degree than in Example 1.

Therefore, is a defined composition something in which every element is precisely defined or is it simply something more purified than a cell extract or is a cell extract defined by the process of making. On the web, there are discussions of what "defined composition" is in the context of serum free media. For example "Serum-free medium on the other hand is a more defined medium. While composed of many constituents, the composition is known and the level of each component precisely defined." See http://www.athenaes.com/WhySFM.htm. The specification does not teach or provide any situation where the entire composition is known and the leve of each component precisely defined, but rather teaches fractions from columns, which represent a different sort of composition than the "defined composition" in media.

Finally, using the broadest reasoanble interpretation in concert with ordinary patent law, there is no question that a product by process claim "defines" the product, as noted in MPEP 2113, which notes that 'product-by-process claims are limited by and defined by the process." In the context of the Vind reference, the cell extract is defined by the process of making the cell extract and therefore, may reasonably be deemed a "defined composition" since the composition of the cell extract is defined by the process by which the cell extract is made, as per MPEP 2113 and In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985).

Claim Interpretation

Prior to analysis of the claims under the prior art, the scope and content of the claims must be analyzed. Here, it is the phrase "defined composition" and "consisting essentially of" which must be analyzed. For the reasons given above, the phrase "defined composition" is interpreted to encompass the cell extract of Vind. With regard to the attempt to limit the composition using the phrase "consisting essentially of", MPEP 2111 notes "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Since the specification is entirely silent with regard to the phrase "defined composition" the phrase "consisting essentially of" is simply treated as "comprising". This further supports the rejection since even if the cell extract were deemed not to be a "defined composition", the cell extract certainly comprises a "defined composition" of specific enzymes which function in the instantly claimed methods.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 67, 69-73, 85 and 87-90 are rejected under 35 U.S.C. 102(e) as being anticipated by Vind (U.S. Patent 6,783,941) (who receives benefit of priority to 60/256,018, filed December 15, 2000).

Vind teaches an in vitro method of making linear sequence variants (see column 2, lines 47-67),from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs separated by complementary base pairs (see column 2, lines 47-67, column 4, lines 16-21 and column 7, lines 15-20, where only 70% identity between the strands is required which will inherently include many situations of non-complementary base pairs separated by complementary base pairs) comprising:

a) preparing at least one heteroduplex polynucleotide (see column 2, lines 47-67),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see column 17, example 2, where a cellular extract with the MutS mismatch repair enzymes are used, which

extract will inherently comprise the naturally present exonucleases and polymerases such as Taq polymerase, which has exonuclease activity) and an agent with strand cleavage activity (see column 17, example 2, where the MutH enzyme, part of the MutS mismatch repair system, will also inherently be present and which has strand cleavage activity),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see column 2, lines 47-67, where the enzymes correct the heteroduplex).

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (see column 2, lines 47-67 and lines 45-46, which notes "new permutations of mismatches will be generated in the annealing step of each cycle" and see column 19, example 4, where resulting nucleic acids are recovered by cloning).

With regard to claim 69, Vind teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see column 17, example 2, where the cell extract is added).

With regard to claims 70-72, Vind teaches the addition of Taq DNA ligase (see column 17, example where the cell extract, which inherently includes the Taq ligase, is used).

With regard to claim 73, Vind teaches the MutS system enzymes which includes MutH that will have strand cleavage activity (see column 17, example 2).

With regard to claims 84-86, Vind teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see column 2, lines 61-63, where mismatch repair proteins repair mismatches to form homoduplexes).

With regard to claim 87, Vind teaches performance of the method to generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

With regard to claims 88-89, Vind teaches screening for changed properties of the sequence (see column 9, lines 6-12 and column 7, lines 28-38).

With regard to claim 90, Vind teaches 60% homology can be used which would result in three non-complementary base pairs (see column 7, line 43) and that performance of the method will generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941).

Vind teaches an in vitro method of making linear sequence variants (see column 2, lines 47-67) from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs separated by complementary base pairs (see column 2, lines 47-67, column 4, lines 16-21 and column 7, lines 15-20, where only 70% identity between the strands is required which will inherently include many situations of non-complementary base pairs separated by complementary base pairs) comprising:

a) preparing at least one heteroduplex polynucleotide (see column 2, lines 47-67),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see column 17, example 2, where a cellular extract with the MutS mismatch repair enzymes are used, which extract will inherently comprise the naturally present exonucleases and polymerases such as Taq polymerase, which has exonuclease activity) and an agent with strand cleavage activity (see column 17, example 2, where the MutH enzyme, part of the MutS mismatch repair system, will also inherently be present and which has strand cleavage activity),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see column 2, lines 47-67, where the enzymes correct the heteroduplex)

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (see column 2, lines 47-67 and lines 45-46, which notes "new permutations of mismatches will be generated in the annealing step of each cycle" and see column 19, example 4, where resulting nucleic acids are recovered by cloning).

With regard to claim 69, Vind teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see column 17, example 2, where the cell extract is added).

With regard to claims 70-72, Vind teaches the addition of Taq DNA ligase (see column 17, example where the cell extract, which inherently includes the Taq ligase, is used).

With regard to claim 73, Vind teaches the MutS system enzymes which includes MutH that will have strand cleavage activity (see column 17, example 2).

With regard to claims 84-86, Vind teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see column 2, lines 61-63, where mismatch repair proteins repair mismatches to form homoduplexes).

With regard to claim 87, Vind teaches performance of the method to generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

With regard to claims 88-89, Vind teaches screening for changed properties of the sequence (see column 9, lines 6-12 and column 7, lines 28-38).

With regard to claim 90, Vind teaches 60% homology can be used which would result in three non-complementary base pairs (see column 7, line 43) and that performance of the method will generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Vind does not teach adding the ingredients in the particular order claimed in claim 68.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

9. Claims 75-77 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Arnold et al (WO 99/29902)

Vind teaches the limitations of claims 67, 69-73 and 84-90 as discussed above. Vind expressly suggests that any system which recognizes mismatches in duplex DNA

sequences may be used (see column 5, lines 28-57), but Vind does not agents such as hydroxylamine or intercalating agents to induce heteroduplexes.

Arnold teaches the application of mismatch correction methods such as those of Vind to evolving polynucleotides by performing the steps in claim 66 to heteroduplex parental nucleic acids which are corrected to form a heterogenous population of homoduplex nucleic acids (see page 12, paragraph 3, for example). Arnold expressly teaches the use of in vitro DNA repair systems such as those of Vind (see page 17, line 30 to page 18, line 4).

With regard to claims 75-77, Arnold teaches mutagens such as chemicals like hydroxylamine (see page 10, line 30), intercalating agents (see page 10, line 33 to page 11, line 1) and ionizing radiation (see page 11, lines 1-3).

With regard to claim 80, Arnold teaches the use of E. coli extracts for repair, which will include E. coli Pol 1 (see page 17, line 33).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the mutagents of Arnold since Arnold expressly teaches that the heteroduplex correction method may be performed in vitro and since Vind also teaches enzymatic correction of heteroduplexes to homoduplexes in vitro (see column 2, for example). It would further have been prima facie obvious to use the mutagens taught by Arnold since Arnold teaches that these are known equivalents. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's

disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

10. Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Birkenkamp et al (DNA Research (1995) 2:9-14).

Vind teaches the limitations of claims 67, 69-73 and 84-90 as discussed above. Vind does not teach the use of the T4 mismatch correction system.

Vind expressly teaches that a variety of different mismatch repair systems can be used (see column 5, lines 28-57).

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system in the in vitro mismatch repair method of Vind since Vind notes "The instant invention however utilizes the very base pair mismatch correcting property of the mismatch repair system to generate diversity instead of limiting it (see column 5, lines 39-41)." Vind further notes that "The term "mismatch repair system" shall herein be understood according to the art as a system normally present within cells which recognizes mismatches in duplex DNA

sequences (see column 5, lines 28-30)." So Vind is motivated to use ordinary mismatch repair systems in his diversity generation method and Birkenkamp teaches that the T4 system "In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)" Finally, since Birkenkamp teaches that the T4 system is a known equivalent in the prior art of the other systems detailed by Vind in column 5, this falls within the situation described in MPEP 2144.06, which notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

11. Claims 66-74, 81-82, 85, 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Oleykowski et al (Nucleic Acids Research (1998) 26(20):4597-4602).

Vind teaches the limitations of claims 67-73 and 84-90 as discussed above. Vind does not teach the use of Cel I.

Oleykowski teaches that Cel I is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski in the in vitro mismatch repair method of Vind since Oleykowski states,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for
enzyme mutation detection. The latter is a resolvase which nicks one stand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent
two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski further notes

"Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-rnismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Vind in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is simple, with

low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

Response to Arguments

12. Applicant's arguments filed November 15, 2005 have been fully considered but they are not persuasive.

Applicant argues that the claims, as amended, now require an enzyme different than the Mut system used by Vind. Vind's enzymes achieve the same goal and cleave at mismatches. The claim expressly encompasses "enzyme**S**". The use of the plural in the claim therefore expressly encompasses the systems used in Vind. Applicant's argument relies upon a single enzyme with multiple functions, but the claim clearly permits plural enzymes, which supports the conclusion that Vind anticipates the claims as discussed in the rejection.

Applicant then argues that the Mut system does not "cleave at the mismatched nucleotides". MutS binds to mismatched nucleotides and directs cleavage based upon the location of the mismatched nucleotides. The claim does not require cleavage at any particular location relative to the mismatched nucleotide. Further, depending upon the location of the mismatch, the cleavage may be directly adjacent to the mismatch or slightly further away.

Applicant then argues the issue of "defined composition". That issue is fully addressed by the 35 U.S.C. 112, first and second paragraph rejections and the claim interpretation as discussed above.

Applicant argues that the order of addition is not taught by Vind because the extract. The term "comprising" permits any addition, including repeated addition of the extract. So this argument is not persuasive.

Applicant repeats the argument that because Vind prefers the use of high temperature mismatch repair enzymes, this constitutes a teaching away from the use of CEL 1, T4 Endonuclease VII or other mismatch repair systems which are not high temperature systems. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Vind had a preferred embodiment of using high temperature enzymes, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from such embodiments such as those suggested by Birkenkamp or Oleykowski or Arnold since Vind expressly taught the use of low temperature enzymes as well and since Vind expressly desired to use alternate systems (see column 5, lines 28-57).

Applicant's concluding argument is that enzymes from different species would not be combined. Even accepting this argument on its face, it is clearly incorrect since Vind himself suggests the use of enzymes including human enzymes such as GTBP/p160 (see column 5, line 56) (also known as human MSH6), and Vind teaches

how to clone and use such enzymes in the recombination system at columns 6-10. Therefore, contrary to Applicant's arguments, Vind provides all the methodologies needed to make such extracts. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
12/12/05